PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

REC'D 10 AUG 2005
WIPO PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/012572	05.11.2004	07.11.2003

International Patent Classification (IPC) or both national classification and IPC
C12N15/19

Applicant
NOVARTIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Novak-Giese, S

Telephone No. +49 89 2399-8930

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/012572

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 18-42

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	27,39
	No:	Claims	18-26, 28-38,40-42
Inventive step (IS)	Yes:	Claims	
	No:	Claims	18-42
Industrial applicability (IA)	Yes:	Claims	18-42
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: Database Geneseq, 28 March 2003, "Human fibroblast growth factor 23 polypeptide." Database accession no. ABP58110
D2: WO 02/088358 A (GENEPROT INC.) 7 November 2002
D3: WO 01/66596 A2 (CHIRON CORP.) 13 September 2002
D4: Jonsson K. et al., "Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia", N. Engl. J. Med., **vol. 348**, April 24 2003, pages 1656-1663.

1. Novelty

1.1. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 18-26, 28-38 and 40-42 is not new in the sense of Article 33(2) PCT.

1.2. The document D1 discloses (the references in parentheses applying to this document): the protein sequence derived from human fibroblast growth factor 23 (FGF23), comprising amino acids 177-251 of full length FGF23. also encompassed are methods to produce said polypeptide, uses of the polypeptide and its agonists and antagonists for treating disorders related to FGF23.

1.3. Please note that D2-D4 relate also to FGF23, respectively variants thereof, in the context of diseases linked to mutations or aberrations of this gene. Also encompassed by said documents are diagnostic and therapeutic agents related to the polynucleotides and proteins, including probes and antibodies (see e.g. abstract of D3).

As such, also these documents are prejudicial to the novelty of claims 18-26, 28-38 and 40-42; this is especially true since the claims encompass not further defined fragments of FGF23, thereto hybridizing molecules and bioactive polypeptides having 50% identity.

2. Inventive Step

2.1. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 27 and 39 does not involve an inventive step in the sense of Article 33(3) PCT.

The document D1 is regarded as being the closest prior art to the subject-matter of claims 27 and 39.

The subject-matter of claims 27 and 39 therefore differs from this known FGF23 fragment in that D1 discloses a fragment comprising amino acids 177-251 of the C-terminus.

The problem to be solved by the present invention may therefore be regarded as the provision of an additional C-terminal FGF23 fragment.

The solution proposed in claim 27, respectively 39 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

The provision of an alternative (fragment) requires an advantageous or surprising feature in order to justify an inventive step.
However, no such advantage can be derived from the description and/or in the examples of the patent application.
Both fragments appear to be used in the same medical applications, and no experimental support has been found in the application that the fragment of claims 27 and 39 display any superior quality to the fragments known in the art.

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Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Novak-Giese, S

Telephone No. +49 89 2399-8930

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Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

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	No:	Claims	

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see separate sheet

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